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Comparison of Cardiovascular Risk Factors between Type 1 and Type 2 Diabetes Mellitus

THESIS

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By

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DEDICATION

To all free souls who never compromise the truth.

Science cannot flourish without integrity.

And yet it moves.

—Attributed to Galileo Galilei

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ABSTRACT OF THE THESIS

Comparison of Cardiovascular Risk Factors between Type 1 and Type 2 Diabetes Mellitus

By

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Master of Science in Epidemiology

University of California Irvine, 2018

Professor Nathan D. Wong, Co-Chair

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Background: Diabetes mellitus is associated with increased cardiovascular prevalence and mortality. However, this relationship is different between type 1 and type 2 diabetes mellitus. While classical and diabetes-related cardiovascular risk factors are associated with cardiovascular events in both diabetes type, it is unclear how diabetes type plays a role in the prevalence of these cardiovascular risk factors.

Objective: The objective of this study was to compare cardiovascular risk factors between type 1 and type 2 diabetes mellitus, in adults, performing a novel method for diabetes type classification.

Methods: This is a cross-sectional analysis of participants aged 20 years or older in the National Health and Nutrition Examination Survey (NHANES) 1999-2016 that completed the medical examinations, laboratory tests, and the diabetes questionnaire.
Results: A total of 5347 adult participants (age ≥ 20) with diagnosed diabetes were included. Our algorithm classified 230 as type 1 diabetes and 4677 as type 2 diabetes mellitus cases (remaining 440 were excluded). Higher age, triglycerides level, Body Mass Index, and being from races other than White were indicative of type 2 diabetes mellitus, while longer diabetes duration, higher HbA1c rate, more prevalent of chronic kidney disease and having higher education were more indicative of type 1 diabetes mellitus. Lipid panel disturbances, Chronic Kidney Disease, and insulin resistance appeared more prevalent in type 1 diabetes mellitus cohort as previously described.
Conclusion: The prevalence of cardiovascular risk factors differs by diabetes type and have also attested temporal trends. Diabetes type should be considered in cardiovascular disease risk assessments and preventions.

INTRODUCTION

The incidence and prevalence of diabetes mellitus are on the rise both globally and in the United States [1][2]. In the US, the incidence of diagnosed diabetes is projected to increase from about 8 cases per 1000 in 2008 to about 15 in 2050, and the total diabetes prevalence (diagnosed and undiagnosed cases) is estimated to increase from 14% in 2010 to 21%-33% in 2050 [2]. Therefore, diabetes promises to become an even more significant public health issue with substantial health and economic burden.

Mortality rates for patients with diabetes are significantly higher than the general population due to diabetes complications, while cardiovascular disease (CVD) is the leading cause of death among people with diabetes and accounts for an overwhelming 65-75 % of deaths in this group [3]. The role of diabetes in the pathogenesis of CVD became prominent in 1979, when Kannel et al. identified it as a major risk factor, based on Framingham Heart Study results [4][5]. CVD is still the leading cause of death in both type 1 and type 2 diabetes mellitus (T1DM and T2DM), with at least a two-to-four fold increased risk [6]. Additionally, the increase in the relative importance of diabetes with respect to CVD in comparison with other standard CVD risk factors, reported from the Framingham Heart Study data, highlight the importance of increasing diabetes incidence on the burden of CVD [7].

The previous studies comparing the impact of T1DM to T2DM on cardiovascular mortality are not so many, and the results are hardly comparable, due to specific study criteria. One study reported a similar impact of T1DM and T2DM on CVD mortality in middle-aged subjects [8]. In this study, the authors compared the risk of CVD death

associated with T1DM to that associated with T2DM. All participants were aged 45–64 years and free of CVD at baseline, which was conducted from 1982 to 1984 in East and West Finland, and they were followed up for 18 years. In this study the baseline criteria and follow up time was the same for both T1DM and T2DM cohort, which provided a valid comparison of the impact of diabetes types. But the study included only patients with diabetes for whom the age at onset of diabetes was older than 30 years; therefore, the results are not generalizable to all T1DM and T2DM. Another study, which focused on the trend of all-cause and CVD mortality among patients with T1DM or T2DM from 1998-1999 to 2012-2013, using the Swedish National Diabetes Registry (NDR), reported a decline in the CVD mortality among both groups [9]. In this study, the aim was not to compare CVD mortality between T1DM and T2DM but to study the trend of CVD mortality in each group individually. Therefore, the T1DM and T2DM cohort were each matched with a separate control group, while they had different baseline characteristic from each other (mean age T1DM: 35.3 vs. T2DM: 65.2 years, and diabetes duration T1DM: 20 vs. T2DM: 5.7 years). It is possible to extract from the results of this study that CVD mortality was higher in T2DM cohort vs. T1DM cohort both at the baseline (1998-1999) and at the end of the follow-up period (2012-2013), but the difference could not be considered solely correlated with diabetes type because of other characteristic differences between their T1DM and T2DM cohort, such as age and diabetes duration.

CVD events are more common and occur earlier in patients with diabetes than in nondiabetic populations [10]. The age-adjusted relative risk (RR) for CVD in T1DM reported around ten times that of the general population while subjects with T2DM experience a two-to-four fold increase in the number of cardiovascular events

[10][11][12][13]. Despite the known higher risk of CVD in individuals with T1DM, the longer duration of disease in T1DM than in T2DM and the important differences in the underlying CVD pathophysiology between T1DM and T2DM; CVD prevention approaches for T1DM have been extrapolated in large part from the studies on T2DM [10]. Accordingly, the American Heart Association and American Diabetes Association released a joint statement in 2014, calling for more focused research on T1DM and CVD [10].

T1DM which accounts for ~5-10% of diabetes cases results from the autoimmune destruction of the β-cells of the pancreas, leading to absolute insulin deficiency. T2DM which accounts for ~90–95% of those with diabetes encompasses individuals who have insulin resistance and usually have relative insulin deficiency. To date, there is no validated method to distinguish between types of diabetes in surveys. Traditionally, epidemiological criteria for diabetes type classification has been diagnosis at 30 years of age or younger for T1DM. But it has been shown recently that around 40% of T1DM occurs after age 30 years [14]. Additionally, T2DM, which traditionally developed in adults over age 40, is now increasing in adolescents and young adults [15] [16][17]. Therefore, the age at diagnosis poorly differentiates the two types of diabetes and can lead to critical misclassification and biases.

We found two literature reviews which had compared the classical CVD risk factors between T1DM and T2DM [10][6]. Their qualitative results are similar but include some differences. While Duca et al. concluded that the risk factors for CVD are similar in both groups, Ferranti et al. declared better development of specific CVD risk-estimation for T1DM as one of the research gaps which deserves attention [10][6]. Of course, these two reviews summed up studies which either focused only on T1DM or

T2DM cohorts or classified T1DM and T2DM differently and mainly based on the diagnosis age. Therefore, it was of interest in this study to compare the cardiovascular disease risk factors between T1DM and T2DM in US adults with diagnosed diabetes in the same cohort, while implementing a more precise T1DM and T2DM identification strategy which is independent of diagnosis age.

OBJECTIVE

The main objective of the study is to compare classical and diabetes-related CVD risk factors between patients with T1DM versus those with T2DM, among US adults with diagnosed diabetes. We hypothesized that CVD risk factors are different in those with T1DM vs. T2DM. We expect to observe lower insulin resistance, obesity and dyslipidemia and higher hypertension and dysglycemia in T1DM, while having approximately the same level of chronic kidney disease (CKD) and inflammation in both.

METHODS

Study Population

Data for the current study came from the National Health and Examination Survey (NHANES) 1999-2016. NHANES is a cross-sectional survey conducted by the National Center for Health Statistics, a branch of the Centers for Disease Control and Prevention (CDC) [17]. All methods were performed in accordance with the Declaration of Helsinki regarding ethical standards for research involving human subjects. NHANES uses a complex, multistage and stratified sampling design to select a sample representative of the civilian and non-institutionalized resident population of the United States [18]. Since 1999, the survey is called continuous NHANES, because it has been moved to continuous data collection in two-year cycles. Subsequently, around 5,000 participants were interviewed and examined annually and the survey data released on a 2-year cycle [19]. For this investigation, we used all available continuous NHANES cycles from 1999 to 2016, extracting adults aged 20 years or older with diagnosed diabetes and valid diabetes-related data [18].

Dependent and Independent Variables

In the current study, we focused only on diagnosed diabetes as a self-reported diagnosis by the participants. The NHANES surveys assessed participants for diagnosed diabetes using the question, “Other than during pregnancy, have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?” [18]. We defined participants with diagnosed diabetes as those who answered “yes” to this question about the presence of diagnosed diabetes, which excluded gestational diabetes mellitus. Age at diagnosis for those defined as having diagnosed diabetes was determined by the

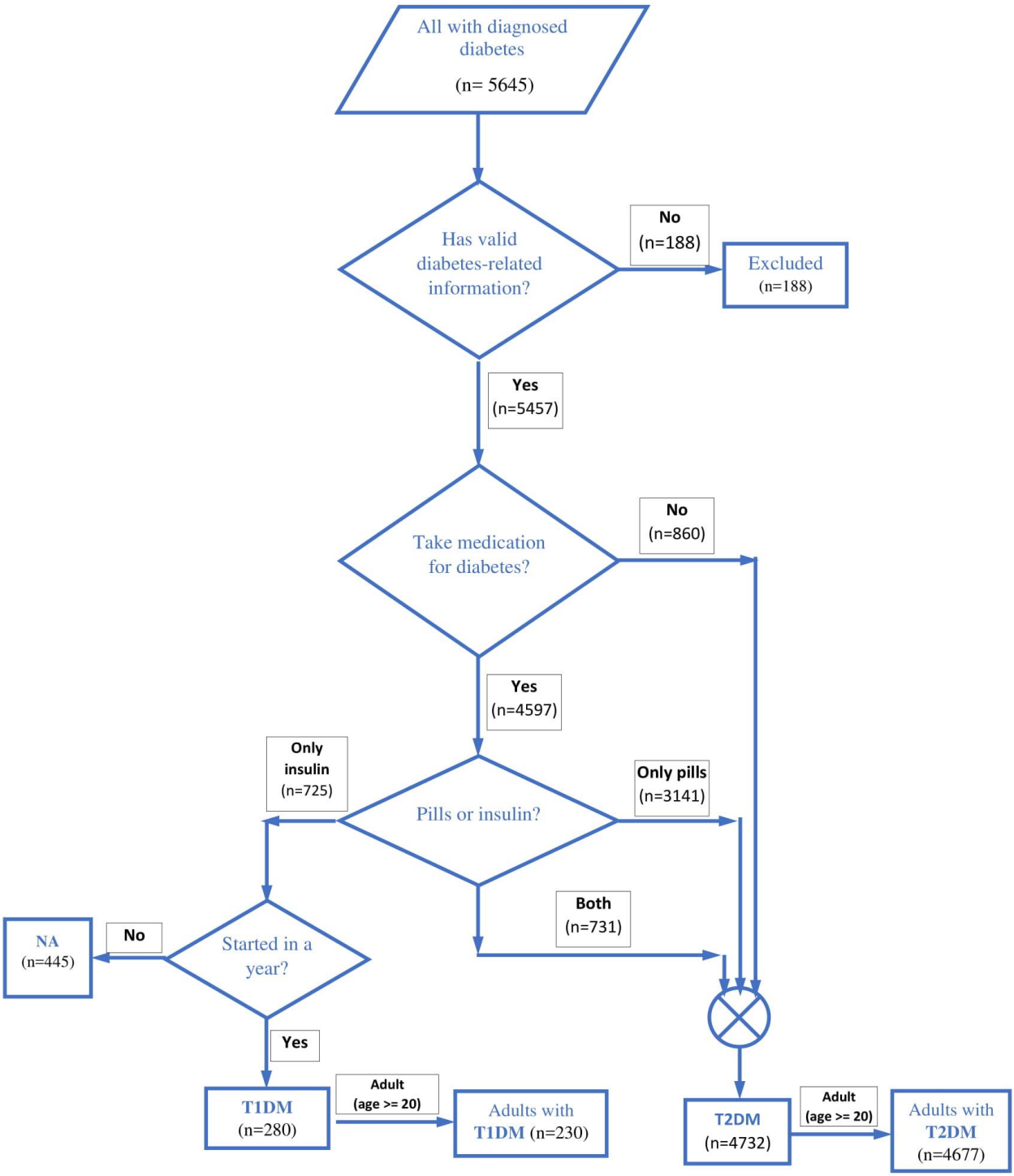
participant's self-report of their age "when a health professional first told you that you had diabetes or sugar diabetes?" [18]. And, diabetes duration was calculated as their age at the time of the survey minus their age at diabetes diagnosis. We further obtained the medication treatment information of survey participants by self-reported answers to questions about taking any pill to lower blood sugar, taking insulin, and if so, for how long taking insulin, and used them for the classification of diabetes type. Participants with diabetes who did not report their age at diagnosis, or medications status, or had invalid data for any of them were excluded (n = 188 for NHANES 1999–2016).

The main dependent variable was the diabetes type. To improve the accuracy of diabetes type identification, we used a set of constraints based on the standard of care treatment strategy differences, without any criteria about the diagnosis age.

Since T1DM and T2DM are pathophysiological distinct diseases, the treatment approaches for each group are considerably different. Based on the American Diabetes Association (ADA) Standard of Medical Care in Diabetes 2018, all patients with T1DM should be treated with insulin, and none of the oral antihyperglycemic agents are FDA-approved for T1DM [20]. Additionally, based on the standard of care, patients with T2DM should start with monotherapy oral antihyperglycemic agents, but in cases of a severe HbA1c level, they would be considered for dual therapy which would be oral antihyperglycemic agents plus insulin [20]. In the longer run (approximate period of 10-15 years), T2DM patients may become completely insulin deficient and need insulin therapy. Some of these patients may discontinue their oral medication at this point, for relief from their adverse effects.

Therefore, we stratified our sample by diabetes type based on the treatment information as shown in **Figure-1**. We defined T1DMs as patients with diagnosed diabetes who were only on insulin therapy and started insulin therapy no later than one year after the diagnosis. Similarly, we defined T2DMs as patients with diagnosed diabetes whose treatment was one of the following: no-medication, taking only oral antihyperglycemic agents, or taking oral antihyperglycemic agents plus insulin. The remaining group would be the patients who were taking only insulin but started insulin therapy later than one year after the diagnosis. This group would either be T1DMs who had not been diagnosed correctly as T1DM at the time of diagnosis and therefore received insulin regimen later than one year, or T2DMs who had become insulin-dependent after a considerable amount of years. It is still possible to classify this group based on how long after diagnosis they started insulin therapy, but to keep our T1DM cohort as pure as possible, we excluded this group from the sample for the main analysis.

Figure 1: The Algorithm for Classification of T1DM and T2DM



For easier reference, we grouped our candidate independent variables into demographic, classical risk factors and diabetes-related blocks:

- Demographic: age, gender, race, education, income, smoking status, insurance status, and Body Mass Index (BMI).
- Classical risk factors: systolic and diastolic blood pressure, pulse pressure, total-cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).
- Diabetes-related risk factors: diabetes duration, hemoglobin A1c (HbA1c), Homeostatic Model Assessment-Insulin Resistance (HOMA-IR), high-sensitivity C-reactive protein (hs-CRP), and estimated Glomerular filtration rate (eGFR).

Demographic characteristics considered in the analyses included age, gender, race or ethnicity, education level, income level, smoking status, insurance status, and body mass index (BMI). Race/ethnicity in NHANES is self-reported as non-Hispanic white, non-Hispanic black, Mexican American, other Hispanic and non-Hispanic other[18]. We classified education levels into three categories as less than high school (less than 9th grade and 9-11th grade), high school graduate (High school graduate/GED or equivalent), and more than high school (Some college or AA degree, College graduate or above). Income levels are based on the measure of income-to-poverty ratio and were classified into (0, 1.30), (1.30, 3.50) and >3.50 according to the Supplemental Nutrition Assistance Program (SNAP, formerly the Food Stamp Program) guidelines by the U.S. Department of Health and Human Service [21][18]. BMI was obtained from the examination section of NHANES, and obesity was calculated as BMI ≥30 kg/m^2 [18].

Systolic and diastolic blood pressure levels in NHANES were measured three to four times by mercury sphygmomanometer using a standard protocol to reduce variability [18]. We calculated our SBP and DBP by averaging the multiple measurements if available. Pulse pressure was calculated as the difference between systolic and diastolic blood pressure levels.

Total cholesterol was measured enzymatically in serum or plasma in a series of coupled reactions that hydrolyze cholesteryl esters and oxidize the 3-OH group of cholesterol [18]. One of the reaction byproducts, H2O2, was measured quantitatively in a peroxidase catalyzed reaction that produces a color. Absorbance was measured at 500 nm. The color intensity was proportional to cholesterol concentration [18].

Triglycerides were measured enzymatically in serum or plasma using a series of coupled reactions in which triglycerides were hydrolyzed to produce glycerol [18]. Glycerol was then oxidized using glycerol oxidase, and H2O2, one of the reaction products, was measured as described above for cholesterol. Absorbance is measured at 500 nm [18].

HDL-C was measured directly in serum. In this method, the apoB containing lipoproteins in the specimen were reacted with a blocking reagent that renders them non-reactive with the enzymatic cholesterol reagent under conditions of the assay [18]. Thus, the Apolipoprotein B containing lipoproteins were effectively excluded from the assay, and only HDL-C was detected under the assay conditions [18].

LDL-C is calculated from measured values of total cholesterol, triglycerides, and HDL-C according to the relationship:

$$[LDL - Chol] = [\text{total Chol}] - [HDL - Chol] - \frac{\text{TG}}{5}$$

Formula-1

where $\frac{\text{TG}}{5}$ is an estimate of very low-density lipoproteins cholesterol (VLDL-C), and all values are expressed in mg/dL [18].

HbA1c is measured in whole blood samples using high-performance liquid chromatography, performed on instruments certified by the National Glycohemoglobin Standardization Program and standardized to the reference method used in the Diabetes Control and Complications Trial [18].

We calculated HOMA-IR based on the Matthews et al. homeostasis model assessment (HOMA) formula:

$$HOMA - IR = \frac{\text{Glucose} * Insulin}{450}$$

Formula-2

in which Glucose and insulin are both during fasting [22]. The fasting plasma glucose is in (mg/dl) and fasting plasma insulin uU/mL, and both are obtained from NHANES laboratory section[18].

hsCRP is quantified by latex-enhanced nephelometry, in which particle-enhanced assays are based on the reaction between a soluble analyte and the corresponding antigen or antibody bound to polystyrene particles [18].

We calculated the estimated Glomerular Filtration Rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation as presented in Formula-3 (19,20):

$$GFR = 141 * \min * \left(\frac{Scr}{\kappa}, 1\right)\alpha * \max\left(\frac{Scr}{\kappa}, 1\right) - 1.209 * 0.993Age * 1.018\ [if\ female] * 1.159\ [if\ black]$$

Formula-3

where;

Scr is serum creatinine in mg/dL,

κ is 0.7 for females and 0.9 for males,

α is -0.329 for females and -0.411 for males,

min indicates the minimum of $\frac{\text{Scr}}{\kappa}$ and 1, which denotes the smaller of the two numbers,

and

max indicates the maximum of Scr/κ and 1, which denotes the bigger of the two numbers.

Chronic Kidney Disease (CKD) was defined as having an eGFR level lower than 60 mL/min/173 m^2.

Statistical Analysis

We performed the analysis in three phases. First, we used our proposed algorithm for classification of DM cases to T1DM and T2DM and examined the demographic, classical CVD risk factors and diabetes-related risk factors of participants by diabetes type. We calculated the 18-year weight based on the NHANES survey weighting instructions and used SAS survey analysis for calculating all means and percentages, incorporating the

proper weight, cluster, and strata parameters [23]. We used bivariate survey analysis, for comparing the demographic, traditional CVD risk factors and diabetes-related factors between diabetes type and considered the factors significantly different at p-values less than 0.05.

Second, using survey logistic regression, we measured the bivariate association of each of the demographic, classical CVD risk factors and diabetes-related variables with diabetes type and tested how adjusting for age, sex, race and diabetes duration alter the bivariate association of these variables with diabetes type. In this phase, we used the standardized values for each cycle for all continuous variables. We compared the unadjusted and adjusted odds ratios for significant association with diabetes type.

Finally, we conducted a stepwise model selection using multivariate survey logistic regression to distinguish which of the demographic, classical CVD risk factors and diabetes-related risk factors remain independently associated with diabetes type after adjusting for other factors. Like the previous phase, the standardized values for continuous variables were calculated for each cycle before combining the cycles. After combining the cycles, we standardized the continuous variables altogether and used these standardized variables for model selection. We considered 0.15 as the cutoff probability for adding variables, and 0.20 as the cutoff probability for keeping the variables in the model.

RESULTS

Using our novel diabetes type identification strategy, from 5347 adults (age ≥ 20) with diagnosed diabetes, we identified 230 adults as T1DM (only on insulin and started insulin therapy within a year after the diagnosis), and 4677 as T2DM (either no medication, or taking only oral anti-hyperglycemic agents or taking both oral anti-hyperglycemic agents and insulin). 440 patients in the remaining group (only on insulin but started insulin therapy later than one year) were excluded.

Table 1 shows the demographic, classical CVD risk factors and diabetes-related risk factors of all adult participants with diagnosed diabetes by diabetes type. Age, diabetes duration, race, gender, BMI (and obesity), HbA1c, triglycerides, HDL-C, and CKD were significantly different between T1DM and T2DM. T1DM participants tended to be younger (~49 years vs. ~60 years, $p<0.001$), consisted of more male (68% vs. 49.2%, $P= 0.04$) and included more White-race (75.8% vs. 60.1%, $p < 0.001$). These demographic differences were all compatible with established epidemiologic information about T1DM and T2DM. Among the risk factors which appeared significantly different between the two groups, T1DMs have longer diabetes duration (~19 years vs. ~10 years, $p < 0.001$) and higher HbA1c (7.99% vs. 7.22%) but lower BMI (29.95 vs. 32.82 Kg/m^2), lower triglycerides level (115.05 vs. 183.66 mg/dL) and better HDL-C level (54.09 vs. 47.01 mg/dL). Both T1DM and T2DM group demonstrated a high level of hsCRP (>3 mg/L) and insulin resistance HOMA-IR level (>1.9). In the lipid panel, we observed no significant difference in LDL-C and total cholesterol between T1DM and T2DM (mean-LDL: 101.45 vs. 105.18 mg/dL, and mean-total-Cholesterol: 184.41, 188.11 mg/dL). Triglycerides and HDL-C appeared significantly different between T1DM and T2DM

(mean-triglycerides: 115.04 vs. 183.66 mg/dL and mean-HDL-C: 54.09 vs. 47.9 mg/dL). The average level of triglyceride demonstrated a normal level in T1DM (115.04 mg/dL), while it appeared high in the T2DM group (183.66 mg/dL)[1].

The unadjusted and adjusted association between each of the independent variables with diabetes type is presented in Table 2. In the bivariate association analysis, age, diabetes duration, education, BMI, HbA1c, HDL-C, triglycerides, and CKD were significantly associated with diabetes type. After adjustment for age, gender, race and diabetes duration, the differences in diastolic blood pressure, pulse blood pressure, and eGFR became significant too. The measure of association altered only considerably after adjustment for the presence of CKD (unadjusted OR=1.72, adjusted-OR=5.27). After adjustment, lower diastolic blood pressure, BMI, triglycerides, and eGFR and higher pulse pressure, HbA1c, HDL-C and more prevalent CKD were significantly associated with having T1DM.

Table 3 summarizes the results for the stepwise model selection for diabetes type as the outcome, and the demographic and the risk factors as independent variables. Age, diabetes duration, HbA1c, race, triglycerides, education level, and BMI were the factors which remained independently associated with diabetes type in the final model. Between all these eight factors, having CKD was associated with the strongest odds of having T1DM (OR= 5.53) followed by longer diabetes duration, where the odds of having T1DM was around 35% greater for every four years longer diabetes duration.

[1] Less than 150 mg/dL of triglycerides is considered normal.

Table 1. Characteristics of Adults with Diagnosed Diabetes in NHANES (1999-2016) Stratified by Diabetes Type

	All DM (n=5347)	**T1DM** (n=230)	**T2DM** (n=4677)	**p-value**
	Mean (±SD)/N (%)	Mean (±SD)/N (%)	Mean (±SD)/N (%)	
Age* (years)	(n=5347) 59.44 (±13.5)	(n=230) 49.24 (±15.5)	(n=4677) 59.86 (±13.2)	<.0001
Diabetes Duration* (years)	(n=5347) 11.61(±12.2)	(n=230) 18.74 (±13.4)	(n=4677) 10.47 (±11.8)	<.0001
Gender*	(n=5347)	(n=230)	(n=4677)	0.040
Female	2652 (50.4)	102 (42.0)	2332 (50.8)	
Male	2695 (49.6)	128 (58.0)	2345 (49.2)	
Race/Ethnicity*	(n=5347)	(n=230)	(n=4677)	<.0001
Mexican American	1134 (8.9)	24 (4.2)	1040 (9.4)	
Other Hispanic	472 (5.9)	6 (1.4)	432 (6.4)	
Non-Hispanic White	1881 (61.1)	115 (75.8)	1610 (60.4)	
Non-Hispanic Black	1456 (16.3)	78 (16.5)	1219 (15.8)	
Other	404 (7.8)	7 (2.1)	376 (8.4)	
Education	(n=5340)	(n=230)	(n=4672)	<0.113
< High school	2136 (27.9)	76 (19.5)	1874 (28.3)	
High school	1183 (24.5)	49 (28.0)	1031 (24.0)	
> High school	2021 (47.6)	105 (52.5)	1767 (47.7)	
Smoking status	(n=5346)	(n=230)	(n=4676)	0.146
Never	2645 (48.5)	106 (45.5)	2332 (49.0)	
Former	1833 (34.5)	71 (30.8)	1585 (34.1)	
Current	868 (17.0)	53 (23.7)	759 (16.9)	
Income to poverty ratio	(n=4817)	(n=209)	(n=4210)	0.265
<1	1192 (17.4)	52 (16.9)	16.98 (17.4)	
1–3.5	2562 (50.5)	107 (43.6)	50.50 (32,4)	
>3.5	1063 (32.1)	50 (39.5)	32.52 (50.2)	

Insurance	(n=4891)	(n=230)	(n=4661)	0.995
Have insurance	4234 (89.5)	205 (89.2)	4029 (89.2)	
No insurance	657 (10.5)	25 (10.8)	632 (10.8)	
Systolic BP	(n=5105)	(n=211)	(n=4486)	
(mmHg)	130.65 (±19.8)	127.66 (±19.7)	130.82 (±19.6)	0.072
Diastolic BP	(n=5038)	(n=204)	(n=4432)	
(mmHg)	69.44 (±12.4)	68.19 (±10.7)	69.85 (±12.3)	0.106
Pulse pressure	(n=5038)	(n=204)	(n=4432)	
(mmHg)	61.11 (±20.4)	58.99 (±21.1)	60.86 (±20.0)	0.341
BMI*	(n=5153)	(n=218)	(n=4531)	
(Kg/m^2)	32.72 (±7.6)	29.95 (±7.1)	32.82 (±7.6)	<.0001
Obesity*	(n=5153)	(n=218)	(n=4531)	
	2865 (59.8)	104 (41.8)	2500 (60.2)	0.0003
HbA1c*	(n=5071)	(n=212)	7.22 (±1.7) (n=4452)	
(%)	7.34 (±1.8)	7.99 (±1.9)		<.0001
HOMA-IR	(n=2083)	(n=66)	(n=1880)	
(uU/mL)(mg/dL)	7.91 (±14.5)	8.41 (±15)	6.98 (±10.2)	0.336
hsCRP	(n=3015)	(n=139)	(n=2627)	
(mg/L)	6.0 (±9.7)	5.82 (±10)	5.76 (±9.6)	0.949
Total cholesterol	(n=4967)	(n=208)	(n=4361)	
(mg/dL)	187.62 (±49.9)	184.41 (±46.5)	188.11 (±50.1)	0.385
Triglycerides*	(n=1764)	(n=55)	(n=1599)	
(mg/dL)	180.21 (±181.6)	115.04 (±113)	183.66 (±188.3)	<.0001
HDL-C*	(n=4966)	(n=208)	(n=4361)	
(mg/dL)	47.36 (±13.9)	54.09 (±17)	47.01 (±13.7)	<.0001
LDL-C	(n=1677)	(n=53)	(n=1520)	
(mg/dL)	104.70 (±35.4)	101.45 (±33.6)	105.18 (±35.2)	0.529
eGFR	(n=5249)	(n=221)	(n=4605)	
(mL/min/1.73 m²)	82.00 (±25.4)	82.60 (±32.7)	83.16(±24.0)	0.427
CKD*	(n=4939)	(n=207)	(n=4335)	
				0.012
No	3835 (80.1)	147 (72.8)	3458 (82.2)	
Yes	1104 (19.9)	60 (27.2)	877 (17.8)	

*Significantly different between T1D and T2D at $p \leq 0.05$

BP: blood pressure; **BMI**: Body Mass Index; **HbA1c**: Glycated Hemoglobin; **HOMA-IR**: Homeostatic Model Assessment-Insulin Resistance; **hsCRP**: high sensitivity C-Reactive Protein; **HDL-C:** High-Density Lipoprotein Cholesterol; **LDL-C**: Low-Density Lipoprotein Cholesterol; **eGFR:** estimated Glomerular Filtration Rate; **CKD**: Chronic Kidney Disease

Table 2. The Bivariate Association between Diabetes Type and Demographic, Diabetes-Related and CVD Risk Factors

	Bivariate Association (unadjusted)		**Bivariate Association** (adjusted for age, diabetes duration, gender and race)	
	unadjusted OR (T1DM vs.T2DM)	**95% CI**	**Adjusted OR** (T1DM vs. T2DM)	**95% CI**
Age*** (per SD= ±13.5 years)	0.46	(0.32, 0.66)	0.35	(0.23, 0.53)
Diabetes Duration*** (per SD= ±12.2)	1.52	(1.28, 1.82)	2.20	(1.89, 2.56)
Gender				
Female (reference)	1		1	
Male	1.21	(0.82, 1.78)	1.32	(0.88, 1.97)
Race/Ethnicity				
Non-Hispanic White (reference)	1		1	
Non-Hispanic Black	0.86	(0.60, 1.24)	0.80	(0.55, 1.16)
Mixed***	0.27	(0.16, 0.46)	0.21	(0.12, 0.36)
Education ***				
< High school (reference)	1		1	
High school diploma	4.51	(1.26, 6.75)	5.66	(1.79, 17.84)
> High school	2.92	(1.89, 10.78)	2.88	(1.01, 8.24)
Smoking status				
Never (reference)	1		1	
Current	0.75	(0.34, 1.64)	1.08	(0.41, 2.85)
Former	1.02	(0.48, 2.16)	1.06	(0.47, 2.39)
Income to poverty ratio				
1–3.5 (middle)(reference)	1			
<1 (in Poverty)	1.16	(0.51, 2.64)	0.94	(0.53, 1.64)
>3.5 (high)	1.21	(0.58, 2.51)	1.10	(0.67, 1.81)

Insurance				
Yes (reference)	1			
No	0.89	(0.33, 2.44)	0.81	(0.29, 2.21)
Systolic BP (per SD= 19.8 mmHg)	0.86	(0.67, 1.10)	1.06	(0.81, 1.38)
Diastolic BP** (per SD= 12.4 mmHg)	0.84	(0.69, 1.02)	0.68	(0.55, 0.84)
Pulse pressure** (per SD= 20.4mmHg)	0.94	(0.74, 1.20)	1.38	(1.05, 1.82)
BMI*** (per SD= ±7.6 Kg/m^2)	0.65	(0.52, 0.80)	0.56	(0.46, 0.69)
HbA1c*** (per SD= ±1.8%)	1.39	(1.23, 1.58)	1.35	(1.17, 1.56)
HOMA-IR (per SD= 14.5 (uU/mL) (mg/dL))	1.15	(0.87, 1.53)	1.11	(0.75, 1.64)
hsCRP (per SD= 9.7 mg/L)	0.92	(0.69, 1.22)	0.83	(0.57, 1.22)
Total cholesterol (per SD= 49.9 mg/dL)	0.81	(0.19, 1.09)	0.72	(0.48, 1.06)
Triglyceride*** (per SD= 181.6 mg/dL)	0.10	(0.02, 0.59)	0.16	(0.04, 0.67)
HDL-C*** (per SD= 13.9 mg/dL)	1.47	(1.26, 1.71)	1. 67	(1.41, 1.98)
LDL-C (per SD= 35.4 mg/dL)	0.87	(0.60, 1.24)	0.72	(0.47, 1.09)
eGFR** (per SD= 25.4 mL/min/1.73 m^2)	0.98	(0.75, 1.28)	0.52	(0.40, 0.67)
CKD***				
No (reference)	1		1	
Yes (CKD stage≥3)	1.72	(1.12, 2.65)	5.27	(3.04, 9.14)

*Unadjusted bivariate association significant at $p \leq 0.05$

** Adjusted bivariate association significant at $p \leq 0.05$

*** Both unadjusted and adjusted bivariate association significant at $p \leq 0.05$

OR: Odds Ratio; **CI**: Confidence Interval; **BP:** blood pressure; **BMI**: Body Mass Index; **HbA1c**: Glycated Hemoglobin; **HOMA-IR**: Homeostatic Model Assessment-Insulin Resistance; **hsCRP**: high sensitivity C-Reactive Protein; **HDL-C:** High-Density Lipoprotein Cholesterol; **LDL-C**: Low-Density Lipoprotein Cholesterol; **eGFR:** estimated Glomerular Filtration Rate; **CKD**: Chronic Kidney Disease

Table 3. The Final Multivariable Regression Model for Diabetes Type (T1DM vs. T2DM)

	OR (T1DM vs. T2DM)	**95% CI**	**Coefficient Estimate**	**P-value**
Age (per SD= ±13.5 years)	0.34	(0.23, 0.52)	-1.07	<.0001
Diabetes Duration (per SD= ±12.2 years)	2.05	(1.51, 2.77)	0.72	<.0001
HbA1c (per SD= ±1.8%)	1.79	(1.24, 2.56)	0.58	0.002
CKD (yes vs. no)	5.53	(2.73, 11.23)	1.71	<.0001
Race (mixed vs. White)	0.12	(0.03, 0.51)	-2.16	0.005
Race **(**Black vs. White)	0.51	(0.19, 1.38)	-0.68	0.181
Triglycerides (per SD= ±181.6 mg/dL)	0.16	(0.04, 0.62)	-1.81	0.008
Education **(**High school vs. < High school)	2.47	(1.04, 5.84)	0.91	0.039
Education (> High school vs. < High school)	1.22	(0.55, 2.66)	0.20	0.620
BMI (per SD= ±7.6 units)	0.69	(0.46, 1.03)	-0.38	0.068

Only covariates that were nominally significant at P < 0.20 are shown.

Full model covariates were age, race, gender, education, smoking, insurance status, income level, diabetes duration, HbA1c, HOMA-IR, SBP, DBP, BMI, hsCRP, TG, HDL-C, LDL-C and CKD.

Model building was based on stepwise selection (cutoff for adding variables: p-Value < 015, cutoff for keeping variables: p-value < 0.20).

Mixed race is the combination of 'Mexican-American', 'Other Hispanic' and 'Other Race' categories.

OR: Odds Ratio; **SD:** Standard Deviation; **BMI**: Body Mass Index; **HbA1c**: Glycated Hemoglobin; **HOMA-IR**: Homeostatic Model Assessment-Insulin Resistance; **hsCRP**: high sensitivity C-Reactive Protein; **TG:** Triglycerides; **HDL-C:** High-Density Lipoprotein Cholesterol; **LDL-C**: Low-Density Lipoprotein Cholesterol; **CKD**: Chronic Kidney Disease

DISCUSSION

To our knowledge, this is one of the first studies to compare the classical and diabetes-related CVD risk factors between T1DM and T2DM quantitatively and in the same cohort. Additionally, our study is the first which, based on the available evidence about wide diagnosis age distribution of T1DM and T2DM patients, does not include diagnosis age as one of the criteria for the classification of T1DM and T2DM.

Epidemiologic studies are generally identifying diabetes type based on diagnosis age of diabetes. Patients with diagnosis age of 30 years or younger are considered T1DM, and the rest are considered T2DM. This traditional paradigm originated from common knowledge that most T1DMs are diagnosed under the age of 30 years, and most T2DMs are diagnosed older than that which is not accurate. Despite the case reports of T1DM diagnosis in ages as old as 60-70, the exact distribution of T1DM across human age-span was not previously determined [24][25][26]. In the most recent study to date, Thomas et al. used a genetic, population-based approach to identify T1DMs genetically over a broad age range (1-60 years) [14]. These genetically defined cases of T1DM were distributed across all ages of diagnosis, with 42% of them were diagnosed when aged 31–60 years. These findings indicate that defining T1DM cohort based only on diagnosis age, as is still common in epidemiologic studies, will misclassify more than 40% of all T1DM cases as T2DM [14].

On the other hand, although in some geographical locations (like Europe), defining T1DM based on diagnosis age could provide an incomplete but at least acceptably pure T1DM cohort, in some others (like the US) the high rate of T2DM among children and adolescents will lead to significant misclassification. Thomas Reinehr, in his review on

T2DM in younger ages, has mentioned that the prevalence of T2DM in children and adolescents in the US is approximately 12:100000, while it is around 2.5:100000 in Europe [15]. Moreover, the National Diabetes Education Program (NDEP) update in 2004 reported that in several clinic-based studies, the percentage of children with newly diagnosed diabetes who were classified as having T2DM had risen to 30%-50% [27]. Considering the high prevalence of T2DM in children and adolescents in the US, the traditional paradigm for case definition of T1DM and T2DM could also lead to significant misclassification by identifying children and adolescents with T2DM in the T1DM cohort. NHANES 1999-2016 includes 646 participants with diagnosed diabetes, whose diagnosis age was younger than 30 years. Among these 646 participants, 350 are not taking insulin at all, and 90 are on both insulin, and oral anti-hyperglycemic medications, which means 440 (~61%) of these 646 participants are certainly T2DM cases, and only 206 (~39%) of them could potentially be T1DM cases. Therefore, in NHANES 1999-2016, at least 61% of diabetes cases who were diagnosed younger than 30 years of age are T2DM cases.

Based on the data stated above[2] and the fact that around 5% of all diabetes cases in the US are T1DM, it is possible to demonstrate that identifying T1DM based only on diagnosis age younger than 30 years will lead to a larger false positive than true positive classification, with a positive predictive value of around 49%. Therefore, classifying T1DM and T2DM cases in public health and research surveillances based solely on the diagnosis age is not a valid strategy [14][28].

[2] distribution of age at diagnosis in T1DM from Thomas et al. study (T1DM: 58% diagnosis-age <30 and 42% diagnosis-age≥ 30 years), and the minimum percentage of T2DM who have been diagnosed younger than age 30 years from NHANES 1999-2016 (61%).

Since it has been known that T1DM may develop at any age, different strategies have been previously used to perform a better diabetes type classification by adding additional criteria to the diagnosis age. These additional criteria have been diverse among different studies; so, apart from their unclarified classification accuracy, the diversity of the methods, makes the study results less comparable.

Menke et al. who had attempted to provide an estimate of the prevalence of T1DM in the US, using NHANES 1999-2010, formulated their classification method by adding the initiation time of insulin therapy after diabetes diagnosis to the diagnosis age criteria [29]. They identified participants to have T1DM if they started insulin within one year of diabetes diagnosis, were currently using insulin and were diagnosed with diabetes under age 30 (*definition-1*) or age 40 (*definition-2*) [29]. They reported the prevalence of T1DM in the US population as 2.6/1000 based on *definition-1* and 3.4/1000 based on *definition-2*. As Menke et al. mentioned, their approach made a higher estimate than the one reported by the "SEARCH for Diabetes in Youth Study". SEARCH, which was a multi-center observational study conducting population-based ascertainment of physician-diagnosed diabetes in youth, identified a T1DM prevalence of 1.5/1000 among youth under the age of 20 years, while the Menke et al. estimate for the same age group was 2.4/1000 [29][30]. The limitations of the Menke et al. approach was that their estimates would have missed T1DM cases starting after the age of 30 (or 40) and included some younger people with T2DMs who required insulin within a year of diagnosis. Our algorithm should be able to improve these limitations because it allows the inclusion of T1DM cases diagnosed at any age and restricts the inclusion of T2DMs who take insulin, by checking the oral medication status. Based on our algorithm, the

estimated prevalence of T1DM, for the 1999-2016 NHANES, was 3.8/1000 (1,113,838 people), which was higher than both Menke et al. estimates (2.6/1000 and 3.4/1000)[29]. Interestingly, when we used our algorithm for the NHANES under 20 years of age category, the prevalence estimate became 1.7/1000 (140,537 people), which is very close to 1.5/1000 reported prevalence of T1DM under the age of 20 years by SEARCH. Additionally, our algorithm identified 5.61% of adults (age ≥ 18 years) with diagnosed diabetes as T1DM which is compatible with the reported prevalence of T1DM among US adults as 5.8%, based on the 2016 National Health Interview Survey (NHIS) data [31]. The average age and gender distribution of our classified T1DM and T2DM groups were also well-matched with the available statistics [31][27].

After the classification, comparing our T1DM and T2DM cohort presented significant differences in the mean age, diabetes duration, BMI, HbA1c, triglycerides and HDL-C, the distribution of race and education and the prevalence of CKD. Unlike our hypothesis, which was based on De Ferranti et al. and Duca et al.'s reviews, we did not observe any significant difference in insulin sensitivity (HOMA-IR), total cholesterol and LDL-C among T1DM and T2DM groups [6][10]. On the other hand, our results presented significant difference in the prevalence of CKD among T1DM and T2DM groups, which was not expected based on the De Ferranti et al. and Duca et al.'s conclusions [6][10].

The findings from the analysis suggested that unlike what we expected, insulin resistance is almost as common in T1DM as in T2DM, and both obesity and insulin resistance are more common in T1DM as they were previously reported. Although T1DM population has known to be not more obese than the general population, two large

T1DM cohort studies, the Pittsburgh Epidemiology of Diabetes Complication Study (EDC, 1950-1980) and the Epidemiology of Diabetes Interventions and Complications study (EDIC, 1994) which is a long-term follow up of the Diabetes Control and Complications Trial cohort (DCCT, 1983–1993) reported significant increase in the prevalence of overweight and obesity in T1DM [32][33][34]. While at EDC baseline (1950), the prevalence of overweight and obesity in T1DMs was lower relative to the general population, Conway et al. reported that the prevalence of obesity (BMI ≥ 30 kg/m^2) in EDC cohort increased from 3.4% in 1986 to 21% in 2007 [32]. Respectively, the prevalence of obesity increased from 1% of subjects at the DCCT baseline (1983) to 31% at EDIC year 12 follow-up (2006) [33][34]. Our results showed an even higher prevalence of obesity, around 42%, in T1DM. The increase in obesity could be associated to both the shift of obesity prevalence in the population overall, and the specific effects of intensive insulin therapy on weight gain as shown in the DCCT, where participants in the intensive therapy arm gained significantly more weight than the participants in the conventional therapy arm [35]. Since obesity is a precursor to insulin resistance, increase in obesity among T1DMs could lead to increase in insulin resistance as well. While T1DM is characteristically a disease of absolute insulin deficiency, and traditionally insulin resistance has not been regarded as a common issue in T1DM as it is in T2DM, there is evidence which conveys that insulin resistance contributes to CHD risk in people with T1DM. The CACTI study which assessed insulin sensitivity and its correlation with coronary artery calcification (CAC)[3] in patients with T1DM and nondiabetic controls, concluded that T1DM patients are insulin resistant compared with

[3] Coronary artery calcification (CAC) is the buildup of calcium in the arteries, which can cause blood vessels to narrow and lead to the development of heart disease.

nondiabetic subjects and insulin resistance predicts the extent of coronary artery calcification [36]. Subsequent observations from the EURODIAB Study also suggested a correlation between insulin resistance and CHD events in T1DM [37]. Despite these results, Ferranti and colleagues' summed up their review with a low score for insulin resistance relative association with CVD events in T1DM in comparison with other risk factors, while mentioning the trend study of obesity and insulin resistance in T1DM as a research gap [10]. Accordingly, our results which showed no significant difference in insulin resistance between T1DM and T2DM could indicate an increase in insulin resistance intensity, prevalence or both among T1DM. Therefore, further investigation is needed to evaluate the probable temporal modifications of obesity and insulin resistance among T1DM and the potential correlation between intensive insulin therapy, which has been the standard of care for more than a decade, and the increase of obesity and insulin resistance in the T1DM cohort.

Duca et al. reported more favorable lipids in T1DM than nondiabetic population and Ferranti et al. specified a low relative association between HDL-C and LDL-C disturbances and CVD events in T1DM [10][6]. Our results showed no significant difference in LDL-C and total cholesterol between T1DM and T2DM, which implies worse results for T1DM than expected based on Duca et al. review [6]. Triglycerides and HDL-C appeared significantly better in the T1DM group. The average HDL-C level was in normal range for both the T1DM and T2DM group, but the average triglycerides level was only normal in the T1DM group. Triglycerides remained independently associated with diabetes type even after adjustment for other factors between diabetes type. Interestingly, studies on triglycerides in T1DM are scarce, and consequently, the de

Ferranti et al. review reported no conclusion for the level of relative association between triglycerides and CVD events in T1DM [10].

In our results, average systolic blood pressure was not significantly different between T1DM and T2DM, and it was higher than normal level (<120 mmHg)[4] in both groups [38]. Considering the younger age of T1DM cohort, at an equivalent age, T1DMs would experience a higher burden of hypertension than T2DMs, which is compatible with the Ferranti et al. comparison that considered higher importance for hypertension in T1DM vs. T2DM as a CVD risk factor [10].

The results also revealed a higher prevalence of CKD in T1DM than in T2DM which was not expected. Although both Ferranti et al. and Duca et al. studies classified the renal disease as a potent CVD risk factors for both T1DM and T2DM, none of them mentioned any considerable difference for this risk factor between T1DM and T2DM [10][6]. Additionally, many T2DM patients often present with renal disease at the time of the diabetes diagnosis, which is not the case in T1DMs; therefore, more renal disease prevalence in T2DM could be expected. Consequently, the higher prevalence of CKD in T1DM in our results also requires further attention.

There are some limitations to our study. We only focused on the self-reported data for identification of diabetes, which means the undiagnosed diabetes cases are not included in this study. The reliance of self-report for diabetes diagnosis and treatment information is a potential limitation that could lead to some level of misclassification due to the inaccuracy of the reports. Additionally, the number of T1DM cases that we had in 'Mexican-American', 'Other Hispanic' and 'Other Race' groups for race/ethnicity

[4] Less than 120 mmHg is the 2017 updated normal level by the American College of Cardiology/American Heart Association Task Force

was small and not comparable with the two other categories (Black and White), so we had to collapse these groups in the analysis and could not provide race-specific information for all the race/ethnicity categories. Finally, NHANES is a cross-sectional survey; therefore, our results are prone to all limitations of cross-sectional study designs like misclassification due to recall bias and lack of temporal relationship between risk factors and outcomes.

CONCLUSION

After 40 years since the role of diabetes in the pathogenesis of CVD was first identified by Kannel et al. based on the evidence from the Framingham Heart Study, CVD remains the main cause of mortality in both T1DM and T2DM. Since the incidence and prevalence of diabetes are increasing globally, there is an urgent need for better understanding and preventing CVD burden among patients with diabetes.

Though the classical CVD risk factors have been previously studied in T1DM and T2DM separately, the comparative study of these risk factors in the same cohort has been missing. Such comparative studies will clarify how these risk factors differ by diabetes type and how they may relate differently to the development of CVD in T1DM and T2DM. Additionally, such studies could reveal the effects that treatment strategies may make on the risk factors and their interactions. More research is needed on the public health interpretation of these differences in classical and diabetes-related risk factors and on their implication for more specific risk factor detection and modification strategies in people with diabetes.

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